Set	Items	Description
S1	16	(HLA OR (HUMAN(W)LEUKOCYTE(W)ANTIGEN?)) (2N) (G (W) (2 OR 3 OR 4 OR 5 OR 6))
S2	7	RD (unique items)
S3	150	((HLA OR (HUMAN(W)LEUKOCYTE(W)ANTIGEN?)) (2N) (G)) (5N) (ISOFORM? OR (SPLIC? (W) (ALTERNATIVE? OR VARIANT?)))
S4	39	S3 NOT PY>1997
S5	18	RD (unique items)
S6	1513	MONOPHOSPHORYL (W)LIPID(W)A
S7	825	S6 NOT PY>1995
S8	3	S7 (S) (VECTOR? OR PLASMID? OR DNA)
S9	1	RD (unique items)
S10	308	S7 (S) (ADJUVAN?)
S11	78	S10 AND (GENE? OR DNA OR CONSTRUCT?)
S12	34	RD (unique items)
S13	34	S12 NOT S9
S14	1587	((NAKED(W)DNA) OR PLASMID? OR VECTOR?) (4N) (LIPID?)
S15	358	S14 NOT PY>1995
S16	26	S15 (S) (GOLD OR PARTICLE?)
S17	8	RD (unique items)
S18	332	S15 NOT S16
S19	0	S18 AND GOLD
S20	108	GOLD (S) LIPID? (S) (DNA OR VECTOR? OR PLASMID? OR CONSTRUCT?)
S21	19	S20 NOT PY>1995
S22	7	RD (unique items)
S23	37	GOLD (S) LIPOSOME? (S) (DNA OR VECTOR? OR PLASMID?)
S24	13	RD (unique items)
S25	2	S24 NOT PY>1995
S26	0	LIPID? (4N
S27	11863	(DNA OR VECTOR? OR PLASMID?) (4N) LIPID?
S28	5418	S27 NOT PY>1995
S29	109	S28 (S) (VACCIN? OR IMMUN?)
S30	65	RD (unique items)
S31	12	S30 AND PLASMID?
S32	53	S30 NOT S31
S33	3	S32 AND VECTOR?
S34	53	S32 NOT S3
S35	50	S32 NOT S33

A novel series of amphiphilic imidazolinium compounds for in vitro and in vivo gene delivery.

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Biochemistry (UNITED STATES) Oct 17 1995, 34 (41) p13537-44, ISSN 0006-2960 Journal Code: A0G
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We have developed three catioinic amphiphiles based on the structure 1-[2-(acyloxy)ethyl]-2-alkyl(alkenyl)-3-(2-hydroxyethyl)imidazolinium chlor ide. Although these three compounds differ only in the structure of the hydrophobic acyl chains, they differ greatly in their ability to mediate in vivo and in vitro gene delivery. Moreover, in vitro efficiency is not predictive of in vivo efficiency. The myristoyl form is the most effective compound in vitro, and the oleoyl form is the most effective compound in vivo. The compounds readily form suspensions in aqueous media, both in the pure form and as mixtures with either cholesterol or dioleoylphosphatidylethanolamine. These suspensions can be sonicated to produce smaller **particles** . **Particle** size, electron microscopy, and the ability to capture glucose suggest that these lipids form liposomes on suspension in aqueous media. When mixed with **plasmid** DNA, the **lipid particles** appear to fuse and form larger **particles** . Fusion is maximal at the critical DNA:lipid ratio where extensive aggregation and precipitation are observed. Therefore, these compounds behave similarly to other cationic liposome-forming lipids upon interaction with DNA.

Cancer gene therapy using plasmid DNA: safety evaluation in rodents and non-human primates.

Parker SE; Vahlsing HL; Serfilippi LM; Franklin CL; Doh SG; Gromkowski SH ; Lew D; Manthorpe M; Norman J

Vical Inc., San Diego, CA 92121, USA.

Human gene therapy (UNITED STATES) May 1995, 6 (5) p575-90, ISSN 1043-0342 Journal Code: A12

Comment in Hum Gene Ther. 1995 May;6(5) 549-50; Comment in Hum Gene Ther. 1995 May;6(5):551-2

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

To evaluate the safety of a **plasmid DNA -lipid** complex, a series of good laboratory practice (GLP) safety studies were conducted with VCL-1005, a **plasmid** DNA expression vector containing both the human class I MHC HLA-B7 heavy-chain and the beta 2-microglobulin (beta 2m) light-chain genes formulated with the cationic lipid, DMRIE/DOPE. In mice, the repeated intravenous injection of VCL-1005 at **plasmid** DNA doses of 0.1, 1.0, or 10 micrograms for 14 days had only incidental effects on clinical chemistry and hematology, and did not result in any organ pathology. Repeated intrahepatic injections of VCL-1005 in mice did not result in significant liver histopathology or significant alterations in liver enzymes. In cynomolgus monkeys, the repeated intravenous administration of VCL-1005 at a cumulative dose of 720 micrograms of DNA had no effects on clinical chemistry, hematology, or organ pathology. Thus, systemic administration of a **plasmid** DNA expression vector containing the coding sequence for a foreign MHC class I molecule did not result in significant toxicity or a pathological **immune** response in animals. These results suggest that the direct transfer of VCL-1005, a **plasmid DNA -lipid** complex, could be used for the safe in vivo delivery of recombinant DNA for a cancer gene therapy trial.

Combined experience from Phase I studies with Allovectin-7, a direct gene transfer immunotherapeutic, in patients with metastatic solid tumors (Meeting abstract).

Nabel GJ; Chang AE; Hersh EM; Vogeizang NJ; Rubin J; Silver H; Stah S; Schreiber AB

Univ. of Michigan Med Center, Ann Arbor, MI

Proc Annu Meet Am Soc Clin Oncol; 14 1995 ISSN 0732-183X

Languages: ENGLISH

Document Type: MEETING ABSTRACTS; CLINICAL TRIAL, PHASE I; CLINICAL TRIAL

Record type: Completed

Gene therapy provides a novel approach to increase tumor cell recognition by the **immune** system through the introduction of **immunogenic** gene products. We report here the combined experience from Phase I trials involving intralesional injections of Allovectin-7 in patients with metastatic melanoma, renal cell or colorectal carcinoma. The gene transfer product is a highly purified DNA **plasmid** driving the expression of encoded sequences for the major histocompatibility complex MHC HLA B-7 heavy chain and beta2 macroglobulin formulated with cytofectin (cationic **lipid vector** , DMRIE/DOPE). Expression of the class I MHC protein on the tumor cell surface is intended to enhance recognition of putative tumor associated antigens and elicit a systemic cell mediated **immune** response which may induce tumor regression. Eligibility criteria include adequate performance status (greater than 70%) and organ function, at least 2 measurable lesions and normal lymphocyte response to PHA stimulation. As of November 1994, 39 patients with either metastatic melanoma (18), renal cell (10) or colon carcinoma (11) were treated at 5 clinical centers out of a total of 72 patients to be enrolled. Dosing regimens comprise escalating single doses or multiple injections of 3 ug to 250 ug Allovectin-7. Injected sites have included subcutaneous nodules, regional lymph nodes and under ultrasound or radiographic guidance lung, liver, mediastinal, renal, periaortic, retrocaval and pancreatic masses. No clinical or laboratory toxicities attributable to the gene transfer product have been observed. Adverse events occurred in 8 out of 39 patients and were attributed either to the underlying disease (2 out of 8) or to the injection and study required biopsy procedures (2 pain, 2 hematoma, and 2 small pneumothoraces after injection of lung nodules). Efficiency of gene transfer is followed

by molecular, flow cytometric and **immunohistochemistry** analyses of biopsies. **Immunological** responses are followed by serology and cytotoxicity assays and **immunocytochemistry** of T lymphocytes subset infiltration in tumor biopsies. As of November 1994, partial tumor regression has occurred in 5 of 11 evaluable patients with metastatic melanoma. These studies indicate that intralesional injection of a **plasmid DNA /lipid** complex can be performed safely and induce tumor regression in some patients.

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Transfecting neurons and glia in the rat using pH-sensitive immunoliposomes

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Neuroscience Letters (NEUROSCI. LETT.) (Ireland) 1995, 184/1 (40-43)
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LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Immunoliposomes were constructed using antibody 5-113 (directed to an antigen on the external surface rat glial cells), the antibody Thy 1.1, and a non-**immune** antibody. The antibodies were conjugated to N-gluytaryl-phosphatidylethanolamine. Liposomes were constructed with these conjugated antibodies, other **lipids** and a beta-galactosidase **plasmid** under the control of the cytomegalovirus promoter. When immunoliposomes decorated with one of three different antibodies were injected into the brain or spinal cord of adult rats, the X-gal reaction product was observed in neurons, astrocytes and vascular elements. There was an increase in neuronal labeling when animals were injected with Thy 1.1 conjugated liposomes and there was an increase in glial labeling in animals injected with 5-113 liposomes. In spinal cords, the immunoliposomes appear to penetrate a substantial distance, transfecting neurons several centimeters from the site of delivery. These data suggest that immunoliposomes may provide an effective transfection system for gene delivery in the CNS.

Cationic lipids direct a viral glycoprotein into the class I major histocompatibility complex antigen-presentation pathway.

Walker C; Selby M; Erickson A; Cataldo D; Valensi JP; Van Nest GV
Chiron Corporation, Emeryville, CA 94608.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Sep 1 1992, 89 (17) p7915-8, ISSN 0027-8424
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Document type: Journal Article
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Recombinant glycoprotein B (gB) of herpes simplex virus (HSV) was processed and presented by class I major histocompatibility complex (MHC) molecules after delivery into cells by using N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium methyl sulfate (DOTAP), a commercially available cationic **lipid** used for **DNA** transfection. Cells treated with DOTAP-associated gB were susceptible to lysis by class I MHC-restricted, HSV-specific cytotoxic T lymphocytes (CTL), and the treated cells restimulated memory gB-specific CTL activity in spleen cells from HSV-infected mice. gB-specific CTL responses were detected in mice **immunized** with recombinant gB and DOTAP but not in those receiving gB emulsified in complete Freund's adjuvant. Thus, cationic lipids may facilitate induction of CD8+ T-cell responses in **vaccinations** with recombinant antigens, and they may serve as readily available reagents for dissecting class I MHC **immunity** to viruses and other intracellular pathogens.